PATENT
Customer No. 22,852
Attorney Docket No. 08702.0020-00000

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	
	)	
VELDMAN et al.	)	Group Art Unit: 1646
	)	
Application No.: 10/688,925	)	Confirmation No.: 2555
	)	
Filed: October 21, 2003	)	Examiner: Kemmerer, Elizabeth C.
	)	
For: NEUTRALIZING ANTIBODIES AGAINST GDF-8 AND USES THEREFOR	)	

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

AMENDMENT AND RESPONSE

In response to the Office communication dated August 2, 2006, the time for responding to which has been extended one month by concurrent filing of a Petition for Extension of Time and fee, please amend the above-identified application as follows.

Amendments to the Claims are reflected in the listing of claims in this paper.

Remarks/Arguments follow the amendment sections of this paper.

Attachments include:

- Alignment of SEQ ID NO:14 and SEQ ID NO:26

AMENDMENTS TO THE CLAIMS:

This listing of claims will replace all prior versions and listings of claims in the application:

1. (Currently amended) An isolated antibody or fragment thereof comprising an amino acid sequence ~~substantially as set out in~~of SEQ ID NO:14, SEQ ID NO:26, or a fragment of SEQ ID NO:14 or SEQ ID NO:26 that is ~~SEQ ID NO:n, wherein n is 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, or 48; and wherein the antibody is~~ capable of specifically binding GDF 8 or BMP 11.

2. (Currently amended) The antibody of claim 1, comprising the amino acid sequence of any one of SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, and SEQ ID NO:36 ~~SEQ ID NO:n, wherein n is 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, or 48~~.

3. (Currently amended) The antibody of claim 1, wherein said antibody is an scFv fragment expressed by E. coli having ATCC Deposit Designation No. PTA 4741~~, PTA 4740, or PTA 4739~~.

4. (Original) The antibody of claim 1, wherein the antibody is capable of specifically binding to a protein comprising the amino acid sequence set forth in SEQ ID NO:54.

5. (Currently amended) The antibody of claim 4, wherein ~~at least~~ SEQ ID NO:54 is characterized by at least one of the following:

(a) the second amino acid ~~from the N terminus~~ of SEQ ID NO:54 is methionine[[,]];

(b) the third amino acid ~~from the N terminus~~ of SEQ ID NO:54 is serine[[, or]]; and

(c) the fifth amino acid ~~from the N terminus~~ of SEQ ID NO:54 is isoleucine~~, independently of each other~~.

6. (Original) The antibody of claim 1, wherein the antibody is human.

7. (Original) The antibody of claim 1, wherein the antibody is IgG_1 or IgG_4.

8. (Original) The antibody of claim 1, wherein the amino acid sequence of the antibody is modified to reduce or alter effector function.

9. (Original) The antibody of claim 8, wherein the amino acid sequence is modified at residues corresponding to amino acid 117 or amino acid 120 of SEQ ID NO:53.

10. (Original) The antibody of claim 1, wherein the antibody is $IgG_{1\lambda}$ or $IgG_{1\kappa}$.

11. (Original) A pharmaceutical composition, comprising the antibody of claim 1.

12.-29. (Canceled)

30. (Currently amended) An antibody produced by the steps of:

(a) providing a starting repertoire of nucleic acids encoding a variable domain which either include a CDR3 to be replaced or lack a CDR3 encoding region;

(b) combining the repertoire with a donor nucleic acid encoding an amino acid sequence substantially as set out in any one of SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, and SEQ ID NO:36, such that the donor nucleic acid is inserted into the CDR3 region in the repertoire so as to provide a product repertoire of nucleic acids encoding a variable domain;

(c) expressing the nucleic acids of the product repertoire;

(d) selecting a specific antigen binding fragment specific for GDF 8; and

(e) recovering the specific antigen binding fragment or nucleic acid encoding the binding fragment ~~the method of claim 29~~.

31.-32. (Canceled)

33. (Original) An isolated antibody against GDF 8, wherein the antibody is capable of inhibiting binding of GDF 8 to ActRIIB.

34. (Currently amended) The antibody of claim 33 comprising the amino acid sequence ~~substantially as set out in~~ of SEQ ID NO:14, SEQ ID NO: 26, or a fragment of SEQ ID NO: 14 or SEQ ID NO:26 ~~SEQ ID NO:n, wherein n is 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, or 48~~.

35. (Currently amended) The antibody of claim 33 comprising the amino acid sequence ~~as set out in~~ of any one of SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:30, SEQ ID NO: 31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, and SEQ ID NO:36 ~~SEQ ID NO:n, wherein n is 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, or 48~~.

36. (Canceled)

37. (Original) The antibody of claim 33 wherein the antibody is capable of specifically binding BMP 11.

38.-40. (Canceled)

41. (Currently amended) An antibody made by the steps of:

(a) culturing E. coli having ATCC Deposit Designation No. PTA 4741 and recovering the expressed Myo29 antibody;

(b) fusing the nucleic acid encoding the svFv of Myo29 with nucleic acids encoding the Fc portion of an immunoglobulin and expressing the fused nucleic acid in a cell; and

(c) germlining the fused sequence ~~using the method of claim 40~~.

42. (Original) An antibody capable of specifically binding to an epitope characterized by the amino acid sequence set forth in SEQ ID NO:54.

43. (New) The antibody of claim 1, wherein the fragment of SEQ ID NO:14 comprises amino acids 1 to 117 of SEQ ID NO:14 (SEQ ID NO:16).

44. (New) The antibody of claim 1, wherein the fragment of SEQ ID NO:14 comprises amino acids 135 to 239 of SEQ ID NO:14 (SEQ ID NO:18).

45. (New) The antibody of claim 1, wherein the fragment of SEQ ID NO:14 comprises amino acids 31 to 35 of SEQ ID NO:14 (SEQ ID NO:31).

46. (New) The antibody of claim 1, wherein the fragment of SEQ ID NO:14 comprises amino acids 50 to 66 of SEQ ID NO:14 (SEQ ID NO:32).

47. (New) The antibody of claim 1, wherein the fragment of SEQ ID NO:14 comprises amino acids 99 to 106 of SEQ ID NO:14 (SEQ ID NO:33).

48. (New) The antibody of claim 1, wherein the fragment of SEQ ID NO:14 comprises amino acids 157 to 167 of SEQ ID NO:14 (SEQ ID NO:34).

49. (New) The antibody of claim 1, wherein the fragment of SEQ ID NO:14 comprises amino acids 183 to 189 of SEQ ID NO:14 (SEQ ID NO:35).

50. (New) The antibody of claim 1, wherein the fragment of SEQ ID NO:14 comprises amino acids 222 to 228 of SEQ ID NO:14 (SEQ ID NO:36).

51. (New) The antibody of claim 1, wherein the fragment of SEQ ID NO:26 comprises amino acids 135 to 239 of SEQ ID NO:26 (SEQ ID NO:30).

REMARKS

With this response, Applicants have canceled claims 12-29, 31-32, 36, and 38-40, amended claims 1-3, 5, 30, 34, 35, and 41, and added new claims 43-51. Upon entry of this Amendment, claims 1-11, 30, 33-35, 37, and 41-51 are pending.

Support for the amended and newly added claims 43-51 can be found, for example, in the original claims and in the specification, and sequence listing as filed. Accordingly, no new matter is added by these amendments.

Restriction Requirement

In the Office communication dated August 2, 2006, requiring restriction and election under 35 U.S.C. § 121, the Examiner requests restriction to one of the following:

I. Claims 1-11, 30, 3-35, 37, 41, and 42, drawn to an antibody;

II. Claims 12-23, 32, and 36, drawn to methods of treatment comprising administering the antibody;

III. Claims 24-29 and 38-40, drawn to nucleic acids encoding an antibody, vectors and host cells comprising the nucleic acid, and methods of recombinantly expressing the antibody; and

IV. Claim 31, drawn to a method of identifying inhibitors.

Applicants provisionally elect to prosecute Group I, claims 1-11, 30, 33-35, 37, 41, 42, and newly added claims 43-51, drawn to an antibody.

The Examiner has further required an election between the following antibody species: SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47; and 48. Applicants provisionally elect to prosecute SEQ ID NO:14, with traverse.

Applicants traverse the election requirement on the basis that a structural and functional relationship exists between the species, and as such, the claims include sufficiently few species that a search and examination would not impose a serious burden on the examiner. Original claim 1 is directed to an antibody comprising sequences that relate to one of three antibodies (Myo29, Myo28, and Myo22). For example, the amino acid sequences of SEQ ID NOs:14, 16, 18, 26, 28, and 30-36 relate to the antibody Myo29, amino acid sequences of SEQ ID NOs: 8, 10, 12, 20, 22, 24, and 37-42 relate to the antibody Myo28, and amino acid sequences of SEQ ID NOs: 2, 4, 6, and 43-48 relate to the antibody Myo22. See Table 1 on page 21 of the specification. With this response, the claims are amended to comprise only the amino acid sequences relating to Myo29. As described in more detail below, the sequences recited in the amended claims are both structurally and functionally related. Accordingly, a search should not pose any burden to the Examiner.

The claimed sequences are functionally related, because when expressed, they share the functional property of binding to GDF-8 or BMP-11. Moreover, all of the sequences recited in the amended claims are structurally related to SEQ ID NO:14. As depicted in Table 1 below, SEQ ID NO:14 is the amino acid sequence for a scFV relating to Myo29. As is well known to those of skill in the art, and described in the specification on page 18, lines 3-7, a scFV comprises a variable heavy (V_H), and a variable light (V_L) chain linked via a polypeptide linker. Here, the scFV for Myo29 (SEQ ID NO:14) comprises a V_H (SEQ ID NO:16), and a V_L (SEQ ID NO:18), connected via a polypeptide linker. As is shown in the table, SEQ ID NO:16 corresponds to amino

acids 1 to 117 of SEQ ID NO:14, and SEQ ID NO:18 corresponds to amino acids 135-239 of SEQ ID NO:14. The V_H of Myo29 comprises three CDRs (designated "H1", "H2", and "H3"), and the V_L of Myo29 comprises three CDRs (designated "L1", "L2", and "L3"), which correspond to SEQ ID NOs:31-33, and SEQ ID NOs:34-36, respectively. Table 1 shows the relationship of these CDRs to SEQ ID NO:14.

TABLE 1

	Myo29	**Relationship to SEQ ID NO: 14**
AA* sequence of scFv	SEQ ID NO:14	
AA sequence of VH	SEQ ID NO:16	AA 1 to 117 of SEQ ID NO:14
AA sequence of VL	SEQ ID NO:18	AA 135 to 239 of SEQ ID NO:14
Germlined AA seq. of scFv	SEQ ID NO:26	Corresponds to AA 1 to 249 of SEQ ID NO:14, but AA 153, 172, 173, 193, and 220 differ
Germlined AA seq. of VH	SEQ ID NO:28	AA 1 to 117 of SEQ ID NO:14
Germlined AA seq. of VL	SEQ ID NO:30	Corresponds to AA 135 to 239 of SEQ ID NO:14, but AA 153, 172, 173, 193, and 220 differ
AA sequence of H1	SEQ ID NO:31	AA 31 to 35 of SEQ ID NO:14
AA sequence of H2	SEQ ID NO:32	AA 50 to 66 of SEQ ID NO:14
AA sequence of H3	SEQ ID NO:33	AA 99 to 106 of SEQ ID NO:14
AA sequence of L1	SEQ ID NO:34	AA 157 to 167 of SEQ ID NO:14
AA sequence of L2	SEQ ID NO:35	AA 183 to 189 of SEQ ID NO:14
AA sequence of L3	SEQ ID NO:36	AA 222 to 228 of SEQ ID NO:14

* AA = amino acid

SEQ ID NO:26 is the germlined version of SEQ ID NO:14, and is thus structurally and functionally related to Myo29. As is shown on the attached sequence alignment, SEQ ID NO:14 and SEQ ID NO:26 differ by only 5 amino acids, none of which fall within the antigen binding domains, and as such, do not alter the functional property of binding to GDF-8 or BMP-11.

Notwithstanding the structural and functional relationship that exists between the claimed amino acid sequences, Applicants note that the M.P.E.P. requires the examination of a reasonable number of sequences, and states that up to ten independent and distinct sequences should be examined without restriction. Manual of Patent Examining Procedure, § 803.04.

Conclusion

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: September 29, 2006

By: J. Amelia Feulner
J. Amelia Feulner
Reg. No. 58,039

ATTACHMENT

SEQUENCE ALIGNMENT OF SEQ ID NO:14 AND SEQ ID NO:26

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Score =  508 bits (1309),  Expect = 1e-142
 Identities = 244/249 (97%), Positives = 246/249 (98%), Gaps = 0/249 (0%)

Query  1    QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQGLEWMGIINPSGGSTSY  60
            QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQGLEWMGIINPSGGSTSY
Sbjct  1    QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQGLEWMGIINPSGGSTSY  60

Query  61   AQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARDENWGFDPWGQGTLVTVSSGGG  120
            AQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARDENWGFDPWGQGTLVTVSSGGG
Sbjct  61   AQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARDENWGFDPWGQGTLVTVSSGGG  120

Query  121  GSGGGGSGGGGSALSYELTQPPSVSVSPGQTASITCSGHALGDKFVSWYQQKPGQSPVLV  180
            GSGGGGSGGGGSALSYELTQPPSVSVSPGQTA+ITCSGHALGDKFVSWYQQ--GQSPVLV
Sbjct  121  GSGGGGSGGGGSALSYELTQPPSVSVSPGQTATITCSGHALGDKFVSWYQQGSGQSPVLV  180

Query  181  IYDDTQRPSGIPERFSGSNSGNTATLTISGTQAMDEADYYCQAWDSSFVFGGGTKVTVLG  240
            IYDDTQRPSGIP-RFSGSNSGNTATLTISGTQAMDEADY+CQAWDSSFVFGGGTKVTVLG
Sbjct  181  IYDDTQRPSGIPGRFSGSNSGNTATLTISGTQAMDEADYFCQAWDSSFVFGGGTKVTVLG  240

Query  241  AAAHHHHHH  249
            AAAHHHHHH
Sbjct  241  AAAHHHHHH  249
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Query = SEQ ID NO:26
Sbjct = SEQ ID NO:14